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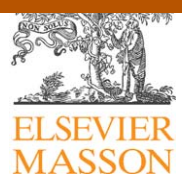

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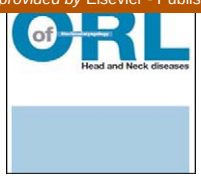

UPDATE

Infantile haemangioma and β-blockers in otolaryngology☆

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KEYWORDS
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Summary Infantile haemangioma (IH) is the most common tumour during early childhood. Although these benign lesions resolve spontaneously, up until recently laryngotracheal sites of IH required invasive management. The dramatic efficacy of β-blockers on IH has radically changed the prognosis. Surgery is now no longer indicated as first-line therapy, but should only be performed for difficult, refractory cases, or in the presence of absolute contraindications to β-blockers. Long-term steroid therapy is also no longer indicated. Propranolol can be used as first-line, single-agent therapy.

Infantile haemangioma (IH), in all sites, is the most common tumour in children. Despite its benign nature and its spontaneously favourable course, IH can sometimes be associated with a severe functional (labial or palpebral sites), cosmetic (thoracic site in young women), and vital prognosis (bleeding, respiratory tract involvement).

Paediatric ENT surgeons are mainly concerned by laryngotracheal haemangiomas. Up until recently, IH of the airways required complex and/or invasive treatments, sometimes associated with temporary tracheotomy.

The dramatic efficacy of propranolol (and β-blockers in general) on infantile haemangiomas, described for the first time in 2008 by a French team, has radically changed the prognosis of these lesions, requiring revision of the previously accepted therapeutic indications [1].

Infantile haemangioma

IH is a benign vascular tumour, rather than a vascular malformation. It has a characteristic histological appearance (typical capillary proliferation) and a specific marker is associated with this tumour: GLUT-1 [2].

IH affects 4 to 10% of infants under the age of one year, and up to 30% of low birthweight preterm infants (less than 1,500 g) [3]. This tumour is more frequent in girls, especially in the context of certain syndromes (PHACES syndrome) [4]. Other risk factors have also been identified: white skin, and antenatal or perinatal hypoxia, especially in the presence of placental abnormalities [5].

The lesion is typically discovered at birth or soon after birth, then rapidly increases in volume during the first year of life, sometimes until the age of 18 months. It then slowly, but constantly decreases in size. The very great majority of lesions have resolved by the age of 7 years, possibly

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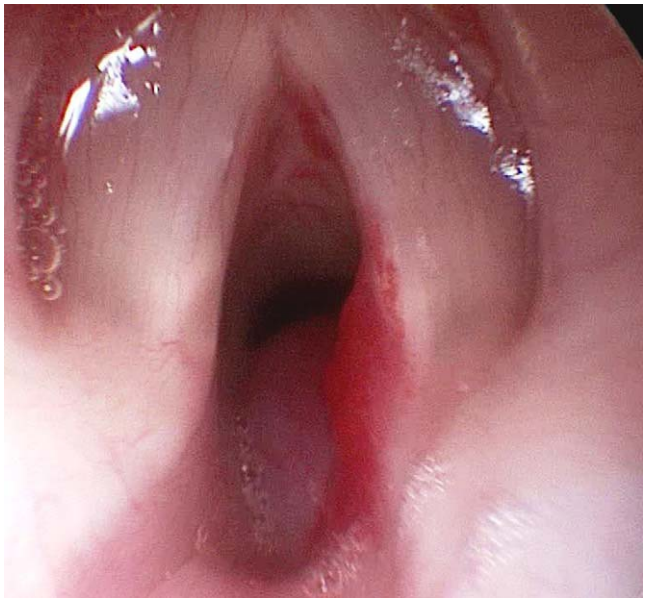

Figure 1 Endoscopic view of the larynx. Glottic (medial edge of the posterior half of the right cord) and posterior subglottic haemangioma.

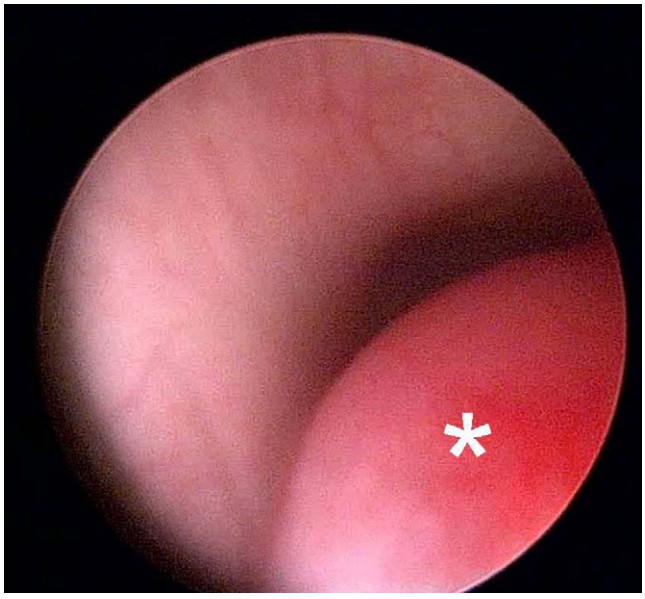

Figure 2 Same patient, rigid 0° 4 mm tracheoscopy: very large right posterior IH (*) causing about 80% obstruction.

leaving only minor cosmetic sequelae: distended skin zones or fibroadipose residues [6]. Prior to the introduction of propranolol, the severe complication rate was estimated to be 10% [7].

IH is the most common tumour of the airway in children. Subglottic lesions are generally responsible for rapid onset of clinical features, as, according to Poiseuille's law, resistance to flow of a liquid in a pipe is equal to the radius raised to the fourth power. This means that if the radius of the airways is decreased by one half, airflow resistance, and therefore the effort required to maintain satisfactory ventilation, increase 16-fold. The subglottic region, physiologically the narrowest segment of the upper airways, is therefore the most likely to be the site of clinical symptoms related to an angiomatous lesion of the airway. The diagnosis is established on complete endoscopy of the airway (Figs. 1 and 2). MRI can be useful to define the extent of very large lesions (Fig. 3).

Prior to the introduction of β-blockers, medical treatment was based on corticosteroids (systemic or topical), vincristine, and interferon, all of which have potentially serious adverse effects. Surgery was performed either via an open approach or by endoscopy (laser). Tracheotomy was required in the most severe cases, despite the higher morbidity and mortality of this procedure in children than in adults [7].

Beta-blockers

Beta-blockers are antagonists of the β-adrenergic effects of catecholamines, with multiple systemic effects (decreased cardiac output, bronchoconstriction, decreased insulin secretion). Most are fat-soluble and have a very good bioavailability. They have been used in therapeutics in children and adults, essentially in cardiology, for more than 50 years [8].

The efficacy of propranolol on cutaneous IH was discovered incidentally in 2008 [1,9] and the first case of successful treatment of laryngotracheal haemangioma was reported the following year [10].

The mechanisms of action of β-blockers on IH have not been fully elucidated. IH is currently thought to be the consequence of pathological neoangiogenesis in reaction to ischaemia of a skin territory during foetal life (systemic ischaemia would explain segmental IH, while localized ischaemia would be responsible for circumscribed IH, predominantly situated on the head [60% of cases] and prominences, representing possible pressure points during the antenatal and perinatal periods). This hypoxic stress

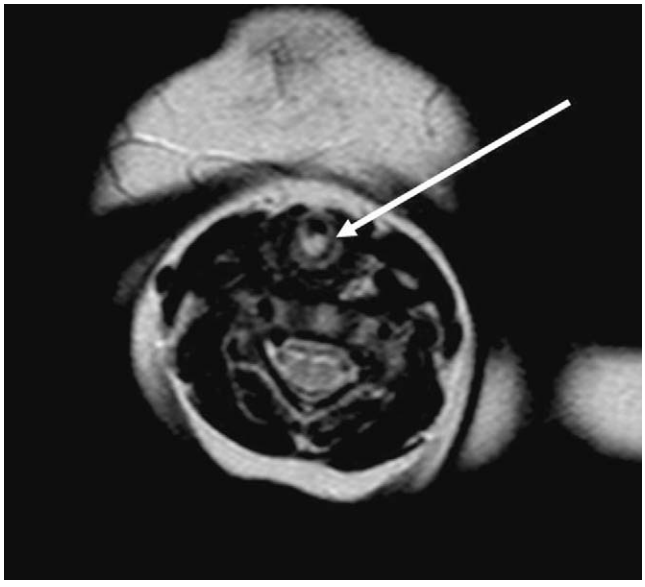

Figure 3 Same patient, cervical MRI, T2-weighted sequence: right posterior tracheal IH with high-intensity signal (arrow).

Table 1 Published reports of cases of IH of the airways treated by β-blockers.

Authors	Year	Number of patients	β-blocker	Dosage (mg/kg/day)
Denoyelle et al. [10]	2009	3	Propranolol	2–3
Buckmiller [23]	2009	1	Propranolol	2
Jephson et al. [18]	2009	1	Propranolol	2
Mistry and Tzifa [24]	2010	1	Propranolol	2
Rosbe et al. [25]	2010	3	Propranolol	1–2
Truong et al. [19]	2010	6	Propranolol	2
Truong et al. [26]	2010	1	Propranolol	2
Maturo and Hartnick [27]	2010	2	Propranolol	2
Blanchet et al. [17]	2010	3	Acebutolol	8
Canadas et al. [15]	2010	1	Propranolol	2
Leboulanger et al. [14]	2010	14	Propranolol + Acebutolol	2–3

would induce the release of pro-angiogenic factors (VEGF, bFGF, etc.) stimulating the proliferation of an endothelial cell clone and resulting in the formation of an IH. Beta-blockers appear to act by inhibiting the secretion of these factors, which stops pathological cell proliferation, and also induces forced apoptosis [5,11–13].

In practice, the efficacy of propranolol on IH is spectacular, as regression of the tumour may sometimes be observed within a few hours after the first dose [1].

Review of the literature and current indications

Efficacy of β-blockers

Many articles reporting the efficacy of β-blockers on laryngotracheal IH have been published since 2009: about 40 cases have been reported (Table 1). The response to treatment, evaluated by clinical examination and especially endoscopic assessment, is rapid and significant (Figs. 4 and 5) [14]. Two treatment-refractory cases in these sites have been reported to date [14,15], including one case after premature discontinuation of treatment. These two patients were subsequently treated by conventional surgical resection. Although it is too early to determine precise figures, β-blockers are considered to be very effective on laryngotracheal IH, but adverse effects of treatment are not rare (at least five out of 40 cases) although benign.

Precautions for use

The protocol of introduction of β-blockers in children with IH was rapidly defined [9]. It consists of looking for any contraindications to treatment (cardiac conduction block,

Figure 4 Endoscopic view of the subglottic region of a 4-month-old female infant with a very large left posterolateral subglottic IH, causing almost 90% obstruction.

Figure 5 Endoscopic view of the subglottic region; same patient as in Fig. 4: appearance of the lesion after 2 weeks of treatment with propranolol. Residual obstruction estimated to be 20%.

ventricular failure, etc.) and detecting any early adverse effects. There is no minimum age for initiation of treatment, but hospitalisation for several days is justified in infants with sometimes severely obstructive lesions. A paediatric cardiology consultation, ECG and echocardiography are required before starting treatment.

Treatment is initiated at a low dose, in three divided doses per day. The starting dosage is usually 0.5 mg/kg per day in three divided doses, but can be increased to 1 mg/kg per day after 48 hours when treatment is well tolerated (surveillance of heart rate, blood pressure, and capillary blood glucose because of the risk of hypoglycaemia) [16]. The dosage is adjusted by steps of 0.5 to 1 mg/kg every 48 hours, as the effective dose is generally situated between 2 and 3 mg/kg per day in three divided doses. An oral suspension form of propranolol, adapted to children, is currently being developed for the French market and should be available soon.

Bronchospasm is generally only observed in children with pre-existing bronchial hyperreactivity [9]. However, a cardioselective β-blocker (acebutolol) can be used, while the concomitant use of inhaled bronchodilators should be limited to patients in whom they are absolutely necessary [17].

Dose and duration of treatment

The effective dose is generally situated between 2 and 3 mg/kg per day in three divided doses. In refractory cases, the dosage can be increased to 4 mg/kg per day in three divided doses. Most authors recommend maintenance of treatment until the end of the IH growth period, i.e. at least until the age of one year for some authors, and until the age of 18 months for most authors, as relapses after premature discontinuation of treatment and cases of secondary resistance have been described [14,15].

Current indications

Although the series published to date are only descriptive case reports, the superiority of β-blockers for the treatment of IH of the upper airways is now generally accepted. To date, about 30 patients treated by β-blockers alone have been reported in the literature, with excellent results [14,18—20].

Beta-blockers are now indicated as first-line treatment for IH in children, with the following exceptions:

- very rare formal contraindications to β-blockers, in which conventional treatment should be preferred;
- small, unilateral, isolated, minimally active subglottic angiomas, in which the benefit—risk ratio of a single endoscopic procedure must be weighed up against that of drug treatment for several months.

A short course of high-dose corticosteroid therapy can be considered in patients with severe respiratory signs, until β-blocker therapy becomes effective. Finally, endoscopic or open surgery may be indicated in acute situations (emergency disobstruction) or to treat cases refractory to β-blockers [20—22].

Propranolol or acebutolol

Very few patients have been treated to date with acebutolol alone, but with good results [17]. As this molecule, with fewer peripheral effects, should theoretically induce fewer adverse effects than propranolol, it could possibly be preferred as first-line treatment. Nevertheless, rigorous clinical trials are necessary to compare the respective efficacy of these two molecules.

Conclusion

Propranolol has transformed the prognosis and management of laryngotracheal IH. Surgery no longer appears to be justified as first-line treatment, but should be reserved for difficult, refractory cases, or in the case of absolute contraindications to all β-blockers. Long-term corticosteroid therapy and prolonged treatment with interferon or vincristine are clearly a thing of the past. Although practice guidelines are still incomplete, the use of β-blockers has considerably simplified the therapeutic management of laryngotracheal IH.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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